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Major Depression in Mothers Predicts Reduced Ventral Striatum Activation in Adolescent Female Offspring With and Without Depression

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Prior research has identified reduced reward-related brain activation as a promising endophenotype for the early identification of adolescents with major depressive disorder (MDD). However, it is unclear whether reduced reward-related brain activation constitutes a true vulnerability for MDD. One way of studying vulnerability is through a high-risk design. Therefore, the aim of the current study was to determine whether reward-related activation of the ventral striatum is reduced in nondepressed daughters of mothers with a history of MDD (high-risk) similarly to currently depressed adolescent girls, compared with healthy controls. By directly comparing groups with a shared risk profile during differing states, we aimed to shed light on the endophenotypic nature of reduced reward processing for adolescent depression. We compared reward-related neural activity through functional magnetic resonance imaging (fMRI) between three groups of female biological offspring ($N = 52$) of mothers with differential MDD status: (a) currently depressed daughters of mothers with a history of MDD (MDD group; $n = 14$), (b) age- and socioeconomic status (SES)-matched never-depressed daughters of mothers with a history of MDD (high-risk group; $n = 19$), and (c) age- and SES-matched control daughters of mothers with no past or current psychopathology in either the mother or the daughter (healthy control group; $n = 19$). For the outcome phase of the reward task, right-sided ventral striatum activation was reduced for both currently depressed and high-risk girls compared with healthy controls. This ventral striatal activity correlated significantly with maternal depression scores. These findings provide further evidence of aberrant functioning for the United States Department of Health & Human Services, National Institutes of Health, National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC)-defined domain of positive valence systems as a vulnerability factor for MDD and a potential endophenotype for the development of depression.

Keywords: adolescent depression, reward function, ventral striatum, at risk design

Adolescent depression is a major public health problem. Adolescents are currently experiencing depression at unprecedented rates (Abela & Hankin, 2008). At any given time, between 4 and 6% of adolescents (typically defined as youth between the ages of 12 and 18) are experiencing major depressive disorder (MDD; Kessler, Avenevoli, & Ries Merikangas, 2001). Lifetime prevalence rates of MDD between the ages of 15 and 18 are estimated to be 14% (Hammen & Rudolph, 2003). Adolescent MDD is associated with significant physical, emotional, and behavioral problems in social, family, school, and other contexts (Goodyer & Sharp, 2005) in addition to suicide-related risk behaviors (Rohde, Beevers, Stice, & O'Neil, 2009; Sharp, Green, Venta, Pettit, & Zanarini, 2012). Early identification and treatment of adolescent depression is therefore essential. This seems to be especially true for adolescent girls, given the robust findings of a significant gender difference in rates of adolescent depression between boys and girls (Forbes & Dahl, 2005, 2012). Cross-sectional (Angold, Erkanli, Silberg, Eaves, & Costello, 2002) and longitudinal (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003) studies have demonstrated increases in rates of depressive symptoms and disorders in girls in early to mid-adolescence until it reaches a 2:1 female to male ratio, which persists throughout the life span (Rudolph, 2009).

A central feature of MDD is a pervasive absence of motivation to obtain reward, low frequency of pursuing rewarding experiences, and reduced enjoyment of rewarding outcomes (Forbes, &

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Dahl, 2005). Rewards are defined as desirable outcomes that serve to influence behavior (Delgado, 2007). Because reward function can be characterized at all levels of analyses, from the molecular to the neural (Sharp, Monterosso, & Montague, 2012), reward-related processing is a promising endophenotype for the early identification of adolescents with MDD. In fact, Hasler, Drevets, Manji, and Charney (2004) identified impaired reward function as meeting more endophenotype criteria (Tsuang, Faraone, & Lyons, 1993) for depression than other putative depressiogenic endophenotypes. The potential of impaired reward function as an endophenotype was first indicated by several studies in adults with MDD that demonstrated reduced activation in response to either reward outcomes or anticipation of reward in the ventral striatum (Kumar et al., 2008; Pizzagalli et al., 2009; Steele, Kumar, & Ebmeier, 2007), caudate (Pizzagalli et al., 2009), the midbrain and hippocampus (Kumar et al., 2008), and the anterior cingulate cortex (ACC; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008).

The downward extension of these findings to children and adolescents has been pioneered by Forbes and colleagues. In a behavioral follow-up study (Forbes, Shaw, & Dahl, 2007), the inability to distinguish between rewards of high and low value predicted MDD symptoms in depressed boys one year after baseline. Three subsequent studies extended these behavioral findings by employing functional magnetic resonance imaging (fMRI). The first of these used a task that required subjects to choose between rewards with varying magnitude of reward probability (Forbes et al., 2006). Compared with healthy controls, children with MDD (9–17 years of age) showed reduced neural responses in the ACC, bilateral caudate, and orbitofrontal cortex during both reward anticipation and outcome. In a second study that used a card-guessing game that also probed reward anticipation and outcome (Forbes et al., 2009), reduced striatal responses in depressed 8–17-year olds were observed, which correlated with lower subjective positive affect in natural environments as measured by a 4-day cell-phone-based ecological momentary assessment.

Taken together, across the adult and adolescent literature, findings converge to suggest that the most robust correlate of depression is reduced activation in the striatum (Forbes & Dahl, 2012). The striatum is the input structure of the basal ganglia and is responsible for the processing of affective stimuli such as rewards (Delgado, 2007). The striatum can be subdivided into two components. The dorsal striatum consists of the dorsal caudate nucleus and putamen and receives extensive projections from dorsolateral prefrontal cortex as well as other surrounding frontal regions. The ventral striatum consists primarily of the nucleus accumbens, along with ventral portions of the caudate and putamen, and receives extensive projections from the ventral frontal regions. The ventral striatum also has extensive connections with limbic areas implicated in emotional processing. The dorsal and ventral striatum are therefore considered to be functionally distinct, with the ventral striatum involved in affective and motivational processing, and the dorsal striatum involved in more cognitive or sensorimotor function (Delgado, 2007; Haber, Fudge, & McFarland, 2000; Strathearn, 2011). Given the affective nature of depression, it is therefore reasonable to expect that the ventral striatum would be especially implicated in depression, although typically, researchers have not subdivided the striatum in their studies of depression.

Another limitation of previous studies of reward function in depression is its correlational nature. Therefore, it remains unclear whether reduced reward processing is a true vulnerability (i.e., a risk biomarker), or a correlate or consequence of adolescent depression. One way of studying vulnerability is through a high-risk design (Goodman & Gotlib, 1999) in which the biological offspring of parents with psychopathology are compared with offspring of parents without psychopathology. Using such a design Gotlib et al., 2010 scanned 13 10–14-year-old, never-depressed daughters of mothers with recurrent depression (high-risk sample) and 13 age-matched, never-depressed daughters with no family history of depression (low-risk sample). Subjects underwent scanning while engaged in a task designed to probe neural responses to reward and punishment outcomes through cues that indicated whether they could win points or avoid losing points if they were fast enough to hit a target. Compared with normal controls, high-risk daughters demonstrated reduced reward processing in the striatum, thereby replicating the overall pattern found in previous studies of adolescents and adults with MDD. These findings mirrored earlier findings by Monk et al. (2008) who compared nucleus-accumbens activation in 17 offspring of parents with a history of depression and 22 offspring of parents without a significant history of psychiatric disorder in response to facial stimuli. Specifically, high-risk offspring demonstrated reduced nucleus accumbens activation to happy faces.

Demonstrating altered reward processing in asymptomatic children with a familial vulnerability for MDD before the onset of their first episode of depression is an important first step toward establishing reduced reward activation as a promising risk biomarker and endophenotype. It may also enhance our understanding of neurodevelopmental mechanisms by which depression is transmitted from mother to daughter. However, it is critical to demonstrate that reduced reward processing in high-risk girls corresponds to or mirrors reduced reward-related processing in *currently depressed* girls. Without the inclusion of a currently depressed comparison group, it is difficult to know whether differences between at-risk girls and healthy controls relate to disease mechanisms associated with MDD. Only by directly comparing groups with a shared risk profile during differing states is it possible to explore whether a specific trait (in this case, disrupted response to reward in the striatum) in the maternal MDD risk condition is present, whether or not there is also ongoing depression in a biological offspring.

Against this background, the aim of the current study was to examine reward-related processing in three carefully assessed groups of female biological offspring of mothers with differential MDD status: (a) currently depressed daughters of mothers who had experienced recurrent episodes of MDD during their daughters' lifetimes (MDD group); (b) age- and SES-matched, never-depressed daughters of mothers who have experienced recurrent episodes of MDD during their daughters' lifetime (high-risk group); and (c) age- and SES-matched daughters of mothers with no past or current psychopathology in either the mother or the daughter (control group). Our focus was on girls only, given the high rates of depression in girls, as discussed earlier. Comparison groups were matched for age, given the known effects for age and depression (i.e., increases in depressive symptoms with age; Angold et al., 2002). Groups were also matched for SES, given the fact that the experimental task was a monetary reward task, and links have been demonstrated between SES and responses to monetary reward in behavioral economic tasks (Camerer, 2003).

We controlled for anxiety symptoms in analyses, given the noted co-occurrence of symptoms of anxiety and depression and potential differential relations with reward function (McClure et al., 2007). Finally, we elected to use the same card guessing game as Forbes et al. (Forbes et al., 2009), because the neural correlates of behavior in this task are well-known in normal adults (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000) and adolescents with MDD (Forbes et al., 2009). Keeping in mind these findings, as well as specific reward function associated with ventral striatum, as discussed earlier, we predicted corresponding reduced activation in both the MDD and high-risk groups in the ventral striatum compared with healthy controls, and that blood-oxygenation-level-dependent (BOLD) activity would negatively correlate with symptoms of depression in offspring. Based on the notion that reduced reward processing may be a heritable mechanism and risk biomarker (Gotlib et al., 2010), we also predicted that BOLD responses in daughters' ventral striata would correlate with MDD symptoms of mothers.

Method

Participants

The study was approved by the local ethics board. Participants were $N = 52$ girls between the ages of 10 and 16 years and included three groups: (a) currently depressed daughters of mothers who had experienced recurrent episodes of MDD during their daughters' lifetime (MDD group, $n = 14$); (b) age- and SES-matched, never-depressed daughters of mothers who had experienced recurrent episodes of MDD during their daughters' lifetimes (high-risk group, $n = 19$); and (c) age- and SES-matched control daughters of mothers with no past or current psychopathology in either the mother or the daughter (healthy control group, $n = 19$). Table 1 summarizes descriptive statistics for the three comparison groups.

Daughters and their mothers were recruited through community advertisements as well as at local clinics serving adolescent populations with emotional problems. To be included in the MDD group, daughters had to have a diagnosis of current MDD as determined by the NIMH-Diagnostic Interview Schedule for Children IV (NIMH-DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab Stone, 2000). Daughters across all three groups were free of current use of nicotine, illicit drugs, psychotic disorders, bipolar I disorder, learning disabilities, and mental retardation as determined by the Wide Range Achievement Test 4 (WRAT4; Wilkinson & Robertson, 2006). For mothers to qualify for the MDD and high-risk groups, they had to have a lifetime diagnosis of recurrent MDD as determined by the Structured Clinical Interview for *DSM–IV*-TR (APA, 2000) Axis I Disorder (SCID; First, Spitzer, Gibbon, & Williams, 2002) and had to have had recurrent MDD during the lifetime of their daughter. Mothers and daughters in the healthy control groups underwent full DISC-IV and SCID assessments, respectively, and were excluded if they met criteria for any other psychiatric disorder (current or lifetime).

Diagnostic Measures

Diagnosis of MDD and comorbid disorders in daughters. The NIMH-DISC-IV (Shaffer, Fisher, Lucas, Dulcan, & Schwab Stone, 2000) was used to determine psychiatric status and MDD in daughters. The DISC-IV is a highly structured clinical interview used to diagnose psychiatric disorders in children and adolescents between the ages of 9 and 17. Although it is designed to be administered by lay interviewers, all adolescents in this study were interviewed by doctoral psychology students or clinical research assistants who had completed training and several practice sessions administering the interview, under the supervision of the first author. The interview is administered following computerized prompts that the interviewer reads out loud. The adolescent's answer is then entered into the program; the program then presents the next appropriate prompt. The interviews were always administered in private, with the interviewer and adolescent facing one another, and the computer monitor within viewing distance of the interviewer.

Table 1
Participant Characteristics

Characteristic	MDD $n = 14$ *M* (*SD*)	High-risk $n = 19$ *M* (*SD*)	Normal control $n = 19$ *M* (*SD*)	Group difference
Daughter age	13.42 (1.78)	13.00 (1.92)	13.71 (1.85)	$F(2) = .52$; $p = .59$
Maternal age	41.35 (8.63)	42.42 (6.42)	41.00 (6.55)	$F(2) = .14$; $p = .86$
Family yearly income	51.42K (48.41K)	63.92K (47.64K)	52.85K (67.13K)	$F(2) = .21$; $p = .80$
Daughter depression (MFQ)	20.07 (12.39)	8.78 (9.12)	7.28 (6.71)	$F(2) = 7.27$; $p = .002$
Daughter anxiety (MASC)	63.21 (21.49)	41.78 (20.10)	41.07 (16.22)	$F(2) = 5.88$; $p = .006$
Maternal depression (BDI)	16.71 (16.76)	15.64 (9.25)	3.64 (3.60)	$F(2) = 5.82$; $p = .006$
Maternal MDD episodes since offspring birth	3.78 (5.20)	5.85 (8.69)	N/A	$F(1) = .58$; $p = .45$
Maternal age, 1st episode	11.42 (13.62)	21.21 (16.25)	N/A	$F(1) = 2.98$; $p = .09$
WRAT	99.25	101.21	106.36	$F(1) = 1.18$; $p = .31$
Ethnicity				
Black	5	2	2	$\chi^2 = 6.40$; $p = .38$
White	5	4	3	
Hispanic	4	7	9	
Asian	0	1	0	
Family history of MDD beyond maternal MDD	4	6	3	$\chi^2 = 3.46$; $p = .48$

Note. MFQ = Mood and Feelings Questionnaire (depressive symptoms of daughters on day of fMRI scan); BDI = Beck Depression Inventory (current depressive symptoms of mothers); MASC = Multidimensional Anxiety Scale for Children; WRAT = Wide Range Achievement Test 4.

Symptoms of depression in daughters. The Mood and Feelings Questionnaire (MFQ; Angold, Costello, Pickles, & Winder, 1987) is a 33-item self-report measure used to screen youth (6–17 years old) for clinically significant indicators and symptoms of depressive disorders. Items were derived from the *DSM–IV*-TR (APA, 2000) depressive disorder criteria and include loneliness, worries about the future, somatic complaints, and tearfulness. Response options include 0 = *never*; 1 = *sometimes*; and 2 = *always*. Excellent psychometric properties have been demonstrated for this measure, including internal consistency (α = .92; Wood, Kroll, Moore, & Harrington, 1995), and were also found for the current study (α = .94).

Symptoms of anxiety in daughters. The Multidimensional Anxiety Scale for Children (MASC; March, 1997) is a 39-item self-report measure used to screen youth (8–19 years old) for anxiety. It contains 5 subscales, including physical symptoms, harm avoidance, social anxiety, anxiety disorders, and separation/panic, as well as total anxiety and inconsistency indices. Youth are asked to rate each item on a scale from 0 (*never true about me*) to 3 (*often true about me*). Adequate to excellent internal consistency has previously been documented for this measure (e.g., α = .6–.9; March, 1997) and excellent internal consistency was found for the current study (α = .92). In the current study, the MASC was used to assess and control for anxiety symptoms among comparison groups.

Level of cognitive functioning in daughters. The WRAT4 (Wilkinson & Robertson, 2006) is a brief achievement test measuring reading recognition, spelling, and arithmetic computation and was used in the current study to exclude subjects who might meet criteria for mental retardation or a learning disability.

Diagnosis of MDD in mothers. The SCID (First, Spitzer, Gibbon, & Williams, 2002) was used to determine presence or absence of MDD in mothers. The SCID is a semistructured interview based on Axis-I psychiatric disorder classification, as described in the *DSM–IV*-TR (APA, 2000). To assess a history of depression and comorbid psychiatric problems in mothers, all SCID modules were used for this study. Excellent interrater reliability has been found between raters for symptom assessment related to various diagnoses (overall κ = 0.85; Ventura, Liberman, Green, Shaner, & Mintz, 1998). Mother and daughter interviews were conducted during the same visit, but in two separate rooms by different interviewers to avoid contamination, and were administered by advanced graduate students in the Clinical Psychology Program at the University of Houston, under the supervision of the first author. The SCID interviews were audio taped; 25% were independently scored by raters blind to the diagnosis of the mother. Kappa was 1.00 for current diagnosis of depression and .81 for past diagnosis of depression.

Symptoms of depression in mothers. The BDI (Beck, Steer, & Brown, 1996) is a 21-item self-report measure used to screen adults for level of depressive symptoms. Scores below 13 are indicative of insignificant or minimal depression, scores between 14 and 19 indicate mild depression, scores between 20 and 28 indicate moderate depression, and scores above 29 indicate severe depression. Respondents are asked to choose one of four statements that best describes depressive feelings and experiences within the last two weeks. Excellent internal consistency has previously been documented for the BDI (e.g., α = .90; (David, Ceschi, Billieux, & Van der Linden, 2008) and was also found in the current study (α = .93).

fMRI Procedures

Experimental task. The task (see Figure 1) was an adaptation of a card-guessing game developed by (Delgado et al., 2000) to probe striatal response to feedback associated with monetary reward. Forbes et al. (2009) adapted the task as an event-related design. Each trial (27 s) included an anticipation and outcome period that are analyzed separately. Trials are presented in pseudorandom order with predetermined outcomes. Subjects are asked to guess whether a card would be higher or lower than 5 on a 9-point scale by pressing the button box (higher vs. lower). During the anticipation phase, subjects were told whether that trial will be a "win trial" or a "lose trial"—this information creates expectation/anticipation of reward or nonreward. Next, the actual number of the card was revealed. During the outcome phase, the subject was then informed whether she won or lost on the trial, or neither (neutral outcome = if the actual card value was 5). Subjects were told that they would receive $1 for each win, lose 50 cents for each loss, and experience no earnings for neutral outcomes. Subjects were unaware of the fixed-outcome probabilities and were led to believe that performance would determine net monetary gain at the end of the game. Following Forbes et al. (2009), only the first half of the trials was analyzed, given known habituation effects in the task; note that "5:24/run" is a time reference, not a ratio ("5:24 min/run").

fMRI signal acquisition. Scanning was performed on a 3.0 Tesla Siemens Allegra (Munich, Germany) scanner. After acquisition of a high-resolution, longitudinal relaxation time (T1)-weighted anatomical scan, subjects underwent whole-brain functional runs of 653 scans each (echo-planar imaging (EPI); gradient-recalled echo; repetition time, 2000 ms; echo time, 40 ms; flip angle, 90°; 64 × 64 matrix; 24 axial slices were acquired parallel to anteroposterior commissural line; voxels were 5 mm cubic) for measurement of the BOLD effect (Ogawa et al., 1992). Head movement was minimized by using head and chin cushions, or a piece of soft nonadhesive, hypoallergenic tape similar to those typically used in hospitals. Noise attenuating earphones were used to dampen noise during all scans. An intercom enabled communication between the experimenter and the adolescent between scans. Adolescents were provided with a squeeze ball to press if they needed to be removed from the scanner anytime during scanning. The actual structural and functional imaging protocol took approximately 26 min to complete (approximately 5 min T1-weighted structural scan and 21 min reward task).

Preprocessing. Imaging data for each subject was preprocessed and analyzed in BrainVoyager QX, Version 2.3 (Goebel, 2006). Head motion correction was performed using trilinear interpolation by spatial alignment of all brain volumes to the first volume by rigid body transformations. Two subjects from the MDD group were noted to have > 2-mm translation/rotation, which resulted in a significant between-groups difference in root-mean-squared (RMS) head-motion parameters (M_{MDD} = 1.34, $M_{high\text{-}risk}$ = 0.69, $M_{controls}$ = 0.57; F = 3.48, p = .04; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). All results remained unchanged when the two subjects were excluded from the analyses or when analyses were adjusted for RMS-movement

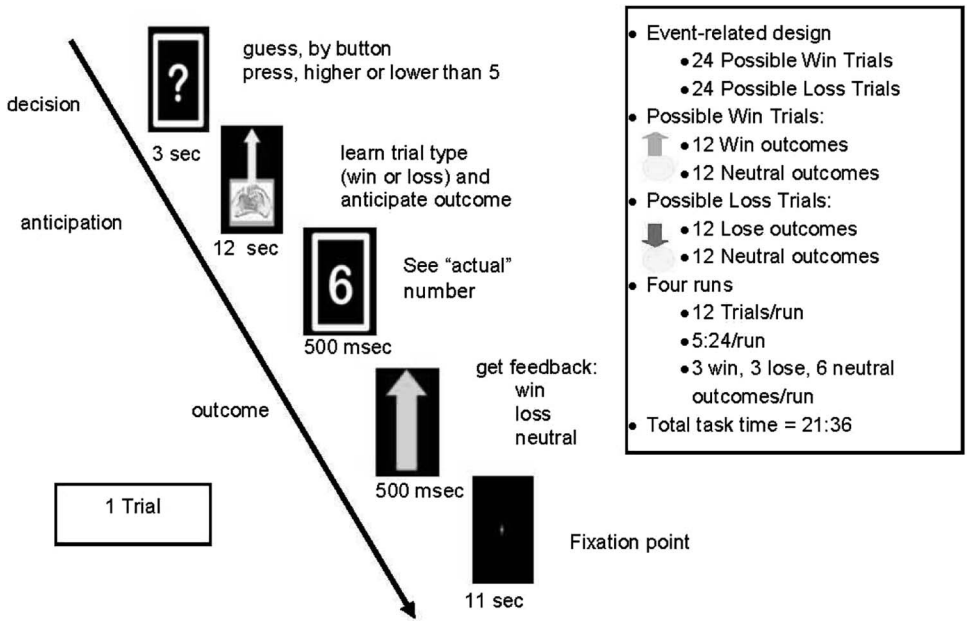

Figure 1. Experimental task.

estimates; hence, all subjects were included to maximize the sample of clinically depressed adolescents. Slice scan time correction was performed using cubic spline interpolation, based on the repetition time (TR) and order of slice scanning (ascending interleaved). Low-frequency, nonlinear drifts of ≤ 2 cycles were removed using a temporal high-pass filter. Spatial smoothing occurred using a Gaussian filter set at 6-mm full-width at half-maximum. The anatomical dataset underwent isovoxel scaling to $1 \times 1 \times 1$-mm resolution via sinc interpolation and was transformed into sagittal orientation. It was then transformed into anterior commissure-posterior commissure (ACPC) and Talairach standard space using cubic spline and trilinear interpolation, respectively. Functional runs for each subject were coregistered with the anatomical 3-dimensional dataset, isovoxel transformed to $3 \times 3 \times 3$-mm resolution, and then transformed into standard ACPC and Talairach coordinate space, resulting in normalized 4-dimensional volume–time course data.

fMRI data analytic strategy. Consistent with previous research that examined early trials for the study of novel reward responses (Forbes et al., 2006; Forbes et al., 2009), the present analyses utilized the preprocessed data acquired from the first half of the experiment. This included 12 possible win trials, of which six had win outcomes and six had neutral outcomes. The analysis included win trials only. BrainVoyager (Goebel, 2006) protocol files were created for the first half of the functional runs of the event-related data, and each predictor was convolved with a double-gamma hemodynamic response function. The resulting reference time courses were used to model the signal time course observed at each voxel. The regression weights for baseline and each condition were estimated using general linear modeling; baseline values represented mean BOLD signals when all predictors were set to zero. The obtained estimates were then *z*-transformed and submitted to second-level random-effects analyses. Consistent with the conventional approach to fMRI analysis (Huettel, Song, & McCarthy, 2009), region of interest (ROI) and whole-brain voxel-wise approaches were used in conjunction. All analyses were performed at two levels: first within the predefined ROI, and then by the whole-brain analyses to evaluate the context and robustness of the ROI results.

ROI analyses. Although the original study by Forbes et al. (2009) was based on a large ROI, which included "the entire bilateral ventral striatum and adjacent regions of the caudate," we chose to look at the left and right ventral striatum specifically, based on research reviewed in the introduction on the functional distinction between ventral and dorsal striata. To test our a priori hypotheses, a mask of each ventral striatum was created by combining substructures of the striatum from the Automated Anatomical Labeling (AAL; Tzourio-Mazoyer et al., 2002) accessed using Wake Forest University's PickAtlas Version 3.0 (Maldjian, Laurienti, Kraft, & Burdette, 2003), and manually adapting the striatum mask to demarcate its ventral portion. The fine-grained editing of the mask was undertaken by tracing visually distinguishable boundaries between the ventral striatum and its adjacent structures in the averaged anatomical images of all subjects combined, following criteria similar to those of Mawlawi et al. (2001). The resulting mask included the nucleus accumbens, ventral caudate, and ventral putamen (Lynd-Balta & Haber, 1994; Mawlawi et al., 2001), and consisted of 108 contiguous voxels on each side of the brain (see inset Figure 2a).

Two contrasts of interest were calculated within this a priori region: (a) reward outcome versus baseline and (b) reward anticipation versus baseline. The between-groups effects for the two contrasts were evaluated in the 2 (reward condition) $\times$ 3 (group status) random-effects ANOVAs, followed by tests of simple effects to decompose the nature of Reward $\times$ Group interaction. False discovery rate (FDR) of $q < 0.05$ was used with a cluster threshold of 100 mm^3 (or $\sim$4 voxels).

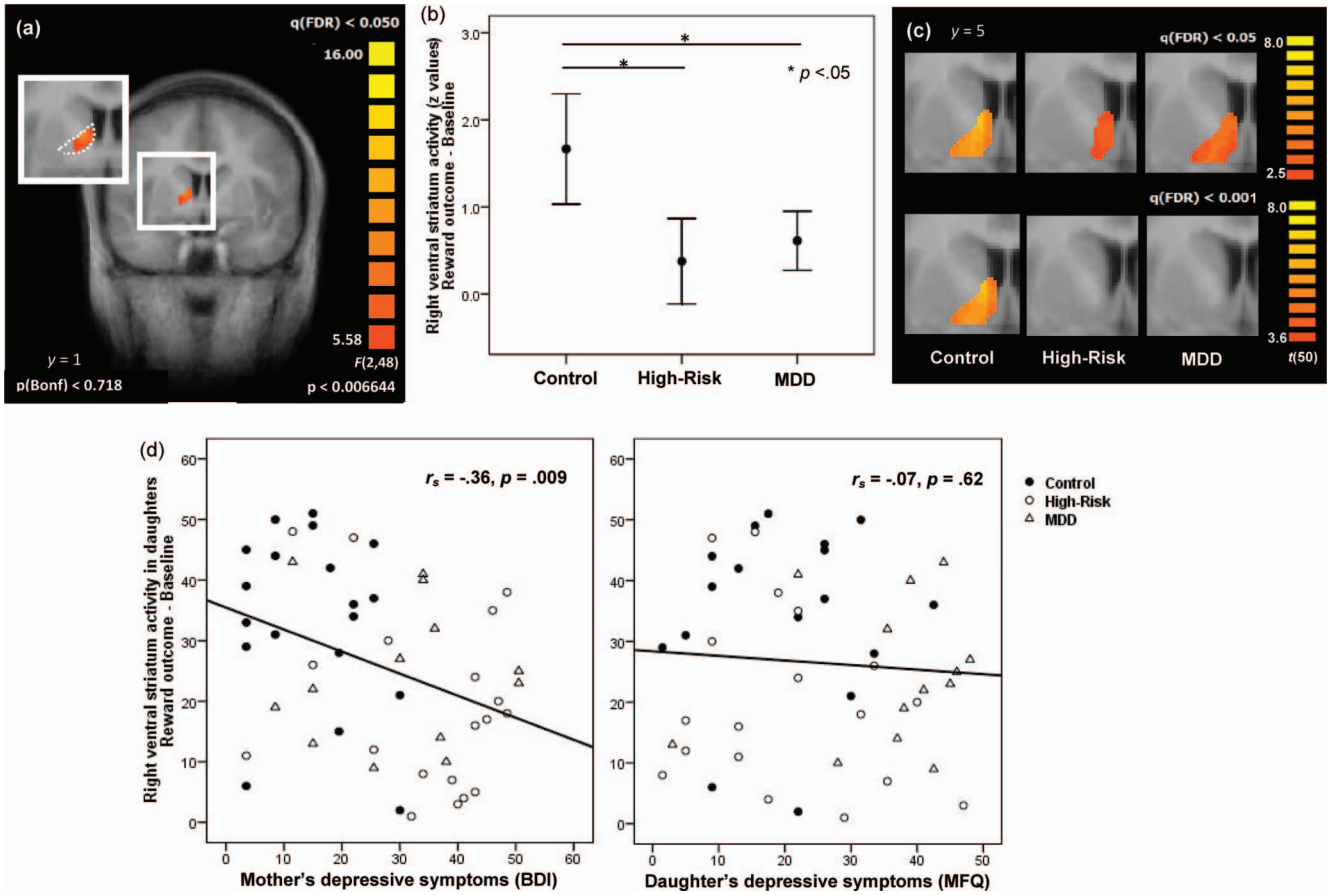

Figure 2. (a) Reward Outcome × Group interaction observed at a subregion (369 mm^3) of the right ventral striatum ($x = 10$, $y = 1$, $z = 10$, $p < .007$, FDR-corrected $q < .05$). Inset of magnified right ventral striatum superimposed on the anatomical mask used to define ventral striatum region of interest; (b) both MDD and high-risk groups show attenuated right ventral striatum activation in response to reward outcome (both $p < .05$; error bars depict 95% confidence interval); (c) activation for the reward outcome versus baseline contrast within the ventral striatum region of interest, presented at FDR-corrected $q < .05$ (top row) and $q < .001$ (bottom row)—the activations are shown at $y = 5$; (d) adolescent daughter's right ventral striatum BOLD response to reward outcome correlates negatively with her mother's depressive symptoms (BDI), but not with her own (MFQ). BOLD signal values were extracted from the anatomically defined right ventral striatum mask for each subject. For graphical representations of Spearman's rank-order correlations, *x* and *y* axes were converted to ranks and are not presented in the original units of measurement.

Associations between reward-related BOLD response and maternal/adolescent depression were further examined in correlation analyses. The BOLD time-course data were extracted from the ventral striatum mask for the contrasts of interest and submitted to correlation analyses with indices of depression severity separately for the mother (BDI) and the daughter (MFQ). Due to the significant non-normality of the BDI and MFQ scores, Spearman's rank–order correlation was used to examine the associations.

The ROI analyses specifically examined the ventral striatum given our a priori hypotheses, but we repeated the analyses using the whole striatum and dorsal striatum masks to confirm the specificity of our findings.

Whole-brain analyses. To examine ROI findings in the context of the whole brain, the random-effects ANOVAs and tests of simple effects, as outlined above, were repeated at the whole-brain level. A cluster threshold of 100 mm^3 (or ~4 voxels) was used to determine clusters of significant activation.

Results

Participant Characteristics

As summarized in Table 1, the three groups were comparable in terms of age, income, ethnicity, and family history of MDD beyond maternal depression (samples were explicitly matched for age and SES). The groups did, as intended, differ significantly in terms of level of daughters' depressive symptoms on the day of fMRI scanning. Post hoc Tukey's tests showed that MDD girls had significantly higher MFQ scores (Angold, Costello, Pickles, & Winder, 1987) than high-risk ($p = .01$) and healthy controls ($p = .003$), but high-risk girls did not differ in MFQ scores from healthy

controls ($p = .91$). A similar pattern of results was observed for symptoms of anxiety, with girls in the MDD group displaying significantly higher MASC ratings than girls in the high-risk group ($p = .01$) and in the healthy control group ($p = .01$). Participants in the high-risk group did not differ in MASC ratings (March, 1997) from those in the healthy control group ($p = .99$). Group differences were also evident for maternal depression with mothers in the MDD group showing higher BDI scores compared with healthy controls ($p = .01$), but not compared with mothers in the high-risk group ($p = .96$). Groups did not differ with regard to family history of MDD, or reading level.

Comorbidities among the girls in the MDD group included separation anxiety disorder ($n = 4$), posttraumatic stress disorder ($n = 2$), obsessive–compulsive disorder ($n = 2$), panic disorder ($n = 2$), social phobia ($n = 3$), specific phobia ($n = 2$), attention deficit hyperactivity disorder ($n = 1$), and conduct disorder ($n = 1$). Daughters in the high-risk group did not meet criteria on the DISC-IV (Shaffer et al., 2000) for any disorder, but showed increased levels of subthreshold symptoms compared with healthy controls. Specifically, 10 participants showed subthreshold symptoms of anxiety disorder, two participants showed subthreshold symptoms of substance-use problems, and seven participants showed no subthreshold symptoms.

Neuroimaging Findings

One participant from the MDD group was found to be an outlier, having had a residual value at the right ventral striatum twice as high as the participant with the second largest value, significantly skewing the distribution of the MDD group (Shapiro-Wilk, $W = .85$, $p = .02$). This participant was hence excluded from subsequent analyses.

Reward outcome. In ROI analyses, the 2 (reward outcome vs. baseline) × 3 (group status) ANOVA yielded a significant interaction effect in a subregion (369 mm^3) of the right ventral striatum ($p < .007$, FDR-corrected $q < .05$, $F = 7.80$, partial $\eta^2 = 0.25$; see Figure 2a). As seen in Figure 2b, the right ventral striatum activity was reduced in both MDD and high-risk adolescents compared with the healthy controls ($t = -3.10$, $p = .005$, Cohen's $d = 1.01$ and $t = -3.38$, $p = .002$, Cohen's $d = 1.13$, respectively); no significant difference was found between the MDD and high-risk groups ($t = .76$, $p = .46$, Cohen's $d = 0.28$). These differences are illustrated in Figure 2c at two different levels of statistical threshold. At the more stringent FDR-correction of $q < .001$, significant ventral striatum activity was only seen in the normal control group.

Although a similar pattern of results was observed in the left ventral striatum ($p < .008$, FDR-corrected $q < .05$), the results, which consisted of a smaller subregion of 5 mm^3, did not survive the cluster threshold correction. Analyses using the whole and dorsal striatum masks yielded no significant findings in the dorsal portion of the striatum, confirming that significant activation was seen only in the ventral striatum.

Activation of all adolescents' ($N = 52$) right ventral striata during reward outcome was negatively correlated with their mothers' depression scores—but not with their own scores, $r_s = -.36$, $p = .009$ (see Figure 2d); and $r_s = -.07$, $p = .62$, respectively. When only the groups with maternal history of depression (i.e., MDD and high-risk groups; $n = 33$) were examined, the correlation between the girls' right ventral striatum activation and adolescent depression scores remained nonsignificant ($r_s = .07$, $p = .70$). The correlation between the daughters' right ventral striatum activity and their mothers' depression scores also dropped to nonsignificance ($r_s = -.11$, $p = .53$).

On whole-brain analysis, the 2 (reward outcome vs. baseline) × 3 (group status) ANOVA yielded no significant findings at a statistical threshold of FDR-corrected $q < .05$. However, a Reward Outcome × Group interaction effect emerged in the right ventral striatum at the less stringent threshold of $p < .005$ (uncorrected). Consistent with the ROI findings and as seen in Figure 3, both MDD and high-risk groups showed an attenuated ventral striatum reward response compared with normal controls. The Reward Outcome × Group interaction effect was also found in several additional regions that were not of a priori interest (see Table 2).

For both ROI and whole-brain analyses, the 2 (reward outcome vs. baseline) × 3 (group status) interaction findings were unchanged when MASC (March, 1997) scores were covaried.

Reward anticipation. The 2 (reward anticipation vs. baseline) × 3 (group status) ANOVA yielded no significant findings, for either the ROI (FDR-corrected $q < .05$) or whole-brain analyses (FDR-corrected $q < .05$ or $p < .005$ uncorrected). However, when the contrast of reward anticipation versus baseline was examined separately within each group, the pattern of results observed was similar to that seen for the contrast of reward outcome versus baseline: Significant activation of the right ventral striatum was seen in normal controls, but not in MDD or high-risk groups, for both ROI and whole-brain analyses (all at FDR-corrected, $q < .05$).

Power analyses. Given the relatively small group sizes, power calculations were conducted on our main finding using GPower (Düsseldorf, Germany). To achieve an $\alpha = .05$ and a power $(1 - \beta) = 0.95$, based on the effect size of $f = .58$ reported in the current study, a total sample size of 42 would be needed to detect differences between the three groups. Therefore, it was determined that our total sample of 52 was adequately powered to detect differences.

Discussion

Previous research has firmly established a correlational, cross-sectional relation between reduced brain activation in reward-related areas and MDD in adults (Knutson et al., 2008; Kumar et al., 2008; Pizzagalli et al., 2009; Steele et al., 2007) and adolescents (Forbes et al., 2009; Forbes, Olino, et al.; Forbes, Ryan, et al.; Forbes et al., 2007; Forbes et al., 2006), especially in the striatum (Forbes & Dahl, 2012). The potential for reduced reward processing to be a risk biomarker of MDD was explored for the first time by Monk et al. (2008) and Gotlib et al. (2010) in a study of high-risk adolescent girls (biological offspring of mothers with a history of MDD) compared with healthy controls. However, without the inclusion of a currently depressed comparison group in these studies, it is difficult to know whether observed differences in reward-related brain activation between at-risk girls and healthy controls reflected disease mechanisms associated with MDD. To this end, the current study aimed to test the hypothesis that corresponding reduced ventral striatal activation would be observed in both currently depressed and high-risk adolescent girls compared with healthy controls. The justification for a focus on the ventral

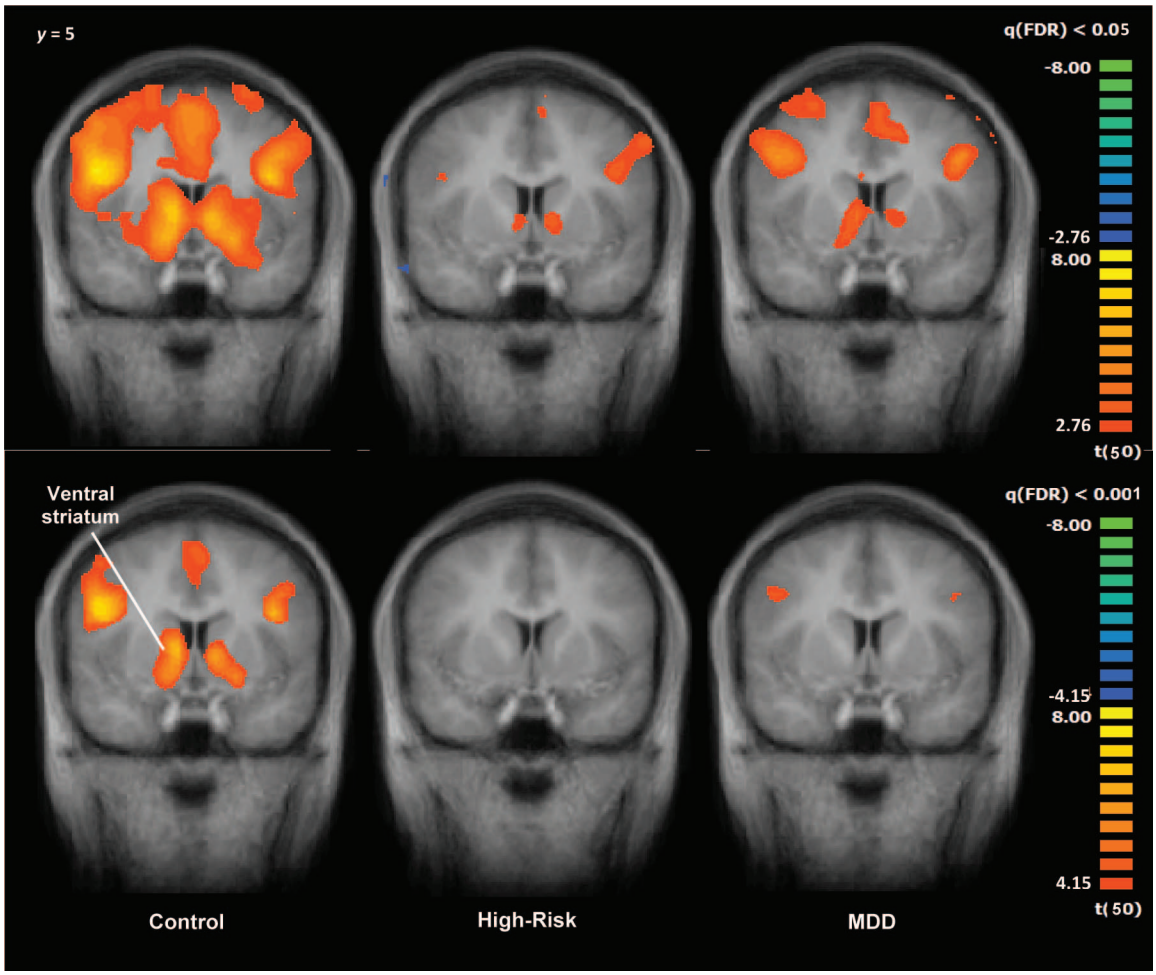

Figure 3. Activation for the reward outcome versus baseline contrast in whole brain analyses, presented at FDR-corrected $q < .05$ (top row) and $q < .001$ (bottom row). Activations are overlaid on the averaged T1 anatomical images of participants. As seen in the top row (FDR-corrected $q < .05$), the ventral striatum activity is reduced in both MDD and high-risk adolescents compared with the normal controls. When examined at a more stringent statistical threshold (FDR-corrected $q < .001$; bottom row), significant activation was only seen in the normal control group.

striatum was based on animal and human studies that have demonstrated distinct functions for the ventral and dorsal striatum, with the ventral striatum involved in affective and motivational processing while the dorsal striatum is involved in more cognitive or sensorimotor function (Delgado, 2007). Given the affective nature of depression, we therefore examined reduced activation in the ventral striatum specifically.

Findings of the current study confirmed hypotheses. For the outcome phase of the task, right-sided ventral striatum activation was reduced for both currently depressed and high-risk girls compared with healthy controls (although whole-brain analyses did not survive strict correction for multiple comparison). Although this finding does not directly address reward processing disruptions as a primarily state-independent endophenotype (such a conclusion would ultimately require repeated scans in the same children), it does provide unique information about this possibility by directly comparing groups with a shared risk profile during differing states. Although highly speculative and in need of further study, the observation that these findings were more prominent on the right side than the left also suggests that early attachment experience may be a contributing factor, with right lateralization of dopaminergic functioning associated with early postnatal experience (Denenberg, 1981; Sullivan & Dufresne, 2006).

The second major finding of the current study was that right-sided striatal activation in the daughters was correlated significantly with the mothers'—but not their own—depression scores. That similar patterns of reward processing are observed in both asymptomatic daughters of mothers with MDD and girls meeting criteria for MDD provides further evidence of aberrant reward functioning as a vulnerability factor for MDD. This finding should be viewed with caution, given the relatively small sample group sizes, nonetheless it underscores the potential role of reduced reward processing as a potential mechanism for the intergenerational transmission of depression from mothers to daughters.

Table 2
Areas of Reward × Group Interaction in Whole-Brain Analyses

Brain region	Hemisphere	Talairach coordinates			Volume (mm^3)	Peak F value	p	Partial η^2
		x	y	z				
Middle temporal gyrus (BA 21)	Right	60	−56	6	524	11.42	0.0001	0.32
Inferior frontal gyrus (BA 9)	Right	38	10	24	672	10.09	0.0002	0.30
Ventral striatum	Right	11	1	9	462	9.92	0.0002	0.29
Inferior frontal gyrus (BA 45)	Right	66	22	6	159	9.74	0.0003	0.29
Inferior parietal lobe (BA 40)	Right	53	−41	24	420	8.98	0.0005	0.27
Supramarginal gyrus (BA 40)	Right	41	−41	33	243	8.80	0.0006	0.27
Medial frontal gyrus (BA 10)	Right	23	46	6	341	8.79	0.0006	0.27
Cingulate gyrus (BA 23)	Left	−1	−23	24	219	7.89	0.0011	0.25

Note. BA = Brodmann's area. Regions with Reward Outcome × Group interaction from whole-brain analyses are shown in descending order of F value. All ps $< .005$ (uncorrected), cluster threshold ≥ 100 mm^3; Talairach coordinates (x, y, z) represent peak voxels in each cluster.

That depression scores of the daughters did not correlate with decreased ventral striatum activity also raises the possibility that *DSM*-based depressive symptoms in adolescents may be less sensitive to variation in striatal activity, and that more nuanced assessments of affect may correlate with brain activity more closely. In the current study, the MFQ (Angold et al., 1987) was administered on the day of scanning, so temporal dissociation does not explain the null finding. While Forbes et al. (2006) demonstrated significant correlations between bilateral caudate activation and scores on a self-report measure of *DSM*-based depression, these correlations were most probably demonstrated as a result of the homogenous nature of their sample (as opposed to the current sample, which included three groups of girls differing on both own status of depression and high-risk status). Moreover, a review of the literature suggests that the use of more nuanced measures of affect may yield more informative results. For instance, Forbes et al. (2009), made use of PANAS-C (Laurent et al., 1999) to assess daily affective variation by cell phone in natural settings and demonstrated correlations with striatal activity. In line with their suggestion, we call for more research that uses *DSM*-based symptom questionnaires alongside assessments of current, momentary affect in natural settings through ecological momentary assessment to provide a more accurate index of true affective experience.

Of note was the fact that group differences could not be demonstrated for the anticipation phase of the task. This finding stands in contrast with Forbes et al.'s (2009) finding of reduced activation in the striatum, which was demonstrated for both anticipation and outcome. An obvious explanation for the null finding in the current study is the differences in a priori regions and comparisons of interest. Forbes et al. (2009) did not subdivide the striatum and also compared healthy controls with currently depressed teens, including both boys and girls, whereas the current study compared currently depressed, high-risk, and never-depressed offspring of mothers. Beyond methodological differences, a more substantive question for future research may also include consideration of how reward anticipation is affected by feedback information from reward outcome. For instance, Olino et al. (2011) recently showed in adolescents that striatal activation patterns associated with depression in the reward anticipation phase of a task depended on the outcome of the previous trial. Therefore, future research may also model information on outcome to examine group differences in anticipation of reward. In addition, the fractionation of reward anticipation may be important for demonstrating group differences in future studies. For instance, in a study of adults, Knutson et al. (2008) showed that depressed and never-depressed participants did not differ in ventral striatum during reward anticipation, but did exhibit increasing anterior cingulate activation during anticipation of increasing gains, whereas never-depressed participants showed increasing anterior cingulate activation during anticipation of increasing loss. Carefully designed experiments that can disentangle different aspects of reward anticipation may therefore clarify mixed findings in this regard.

That biological offspring with the same risk status (i.e., a depressed mother) may demonstrate different behavioral phenotypic profiles (currently depressed vs. nondepressed) despite similar reduced activation in the ventral striatum raises the possibility that protective factors may be at play for high-risk, but currently healthy offspring. Consistent with a developmental psychopathology framework that emphasizes the principle of transactional interactions between risk and protective factors Cicchetti's (2006) and Goodman and Gotlib's (1999) integrative model for the transmission of risk to children of depressed mothers, a range of other factors may interact with a predisposition to reduced reward processing in the development of depression in high-risk offspring. These may include paternal risk and protective factors, child temperament, offspring intellectual and social–cognitive skills, as well as life events and other environmental factors. The current study cannot speak to these factors, so prospective follow-up studies examining environmental factors alongside biological factors are necessary.

Several limitations are of note. The sample size was adequate as demonstrated by our power calculations and larger than Gotlib et al. (2010), but our results should be considered preliminary and call for replication in larger groups of adolescent girls, especially where whole-brain analyses are concerned. The relatively small sample size of the MDD group limited our ability to test developmental effects; and though we matched samples for age, we did not measure puberty. Puberty has recently been shown to be an important predictor of reward-related processing and MDD (Forbes & Dahl, 2010) and should be included in all studies of reward-related decision making in MDD. In addition, an important limitation of the current study was the lack of longitudinal data. Only through a prospective design can the status of reduced reward processing as an early biological marker be fully established.

Despite these limitations, the current study has made a valuable contribution by providing support for reduced reward-related pro-

cessing as an important risk biomarker or endophenotype and neurobiological mechanism in the intergenerational transmission of MDD from mothers to daughters. Endophenotypes are defined as the "measurable components unseen by the unaided eye along the pathway between disease and distal genotype" (Gottesman & Gould, 2003). To be considered an endophenotype, a feature should be measurable, reproducible and state-independent, and it should occur at a greater rate in affected probands than in unaffected family members or in the general population (Balanza-Martinez et al., 2008). In this study, we demonstrated these aspects by showing, for the first time, patterns of brain activation in nondepressed probands that correspond with patterns of activation in currently depressed girls, which were state-independent (not correlating with current level of depression). Findings such as those reported here, combined with recent findings that reduced striatal responses are predictive of treatment response in adolescents with MDD (Forbes, Olino, et al., 2010) contribute to the NIMH Research Domain Criteria (RDoC) initiative by characterizing psychopathology based on dimensions of underlying neurobiological function, specifically in the domain of the positive valence system. Demonstrating aberrations in the positive valence system, specifically during adolescence when stimuli marked by uncertainty acquire unmatched potency to enhance arousal and motivate behavior (Ernst, 2012), is particularly important to advance knowledge about the etiology and development of reward-related psychopathology.

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